PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
CHRISTOPHER L. CURFMAN
BALLARD SPAHR ANDREWS & INGERSOLL, LLP
SUITE 1000, 999 PEACHTREE STREET, N.E.
ATLANTA, GA 30309

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing *(day/month/year)*	24 SEP 2009
Applicant's or agent's file reference 21101.0149P1	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 09/39508	International filing date *(day/month/year)* 03 April 2009 (03.04.2009)
Applicant UNIVERSITY OF UTAH RESEARCH FOUNDATION	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 8270

   For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/220 (January 2004)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 21101.0149P1	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 09/39508	International filing date *(day/month/year)* 03 April 2009 (03.04.2009)	(Earliest) Priority Date *(day/month/year)* 03 April 2008 (03.04.2008)
Applicant UNIVERSITY OF UTAH RESEARCH FOUNDATION		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☒ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☒ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 09/39508

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Group I+: claims 1-22, drawn to a method of screening compounds for anticancer activity. The first invention encompasses a method wherein the compound the compound is (E)-(3-methyl)phenyl]-sulfonyl]-2-propennitril). Additional small molecules will be searched for an additional fee. Should Applicant have additional small molecules searched, Applicant must specify them. The exact claims searched will depend on the specifically elected small molecule.

Group II+: claims 23-78, drawn to a composition comprising a JNK activator and NF-kappa B inhibitor, and using said composition.Should Applicant pay an additional fee(s), Applicant must specify small molecules to be searched. The exact claims searched will depend on the specifically elected small molecule.

----------continued in Supplemental Box ----------

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Group 1: Claims 1-22 restricted to (E)3-(4-methyl)phenyl]-sulfonyl]-2-propenenitrile), i.e. claims 1-9, 11-18, 20-22

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 09/39508

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/10; A61K 31/04; A61K 31/015 (2009.01)
USPC - 514/709; 514/740; 514/764
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC- 514/709; 514/740; 514/764

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC- 514/341; 514/706 (text search)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Electronic Data Bases: (PGPB, USPT, EPAB, JPAB); Google Scholar: NF-kappa B (NF-kB) inhibitor, TNF alpha, JNK, cancer, BAY 11-7082, troglitazone, (E)3-[(4-methyl)phenyl)-sulfonyl]-2-propenenitrile)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	PIERCE et al. Novel inhibitors of cytokine-induced IkappaBalpha phosphorylation and endothelial cell adhesion molecule expression show anti-inflammatory effects in vivo. Jour Biol Chem 22 Aug 1997, 272(34):21096-21103; pg 21096 right col para 2-3, pg 21098 fig 1	1, 3, 5, 7-9, 11-18 ---------- 2, 4, 6, 20-22
Y	US 2005/0124590 Al (KUWADA) 9 Jun 2005 (09.06.2005) para [0005], [0235]-[0236], [0240], claim 53	2, 4, 6
Y	GHANIM et al. Suppression of nuclear factor-kappaB and stimulation of inhibitor kappaB by troglitazone: evidence for an anti-inflammatory effect and a potential antiatherosclerotic effect in the obese. J Clin Endocrinol Metab Mar 2001, 86(3):1306-1312; abstract	20-21
Y	HAZZALIN et al. Anisomycin Selectively Desensitizes Signalling Components Involved in Stress Kinase Activation and fos and jun Induction. Molecular and Cellular Biol Apr 1998, 18(4):1844-1854; abstract	22

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 September 2009 (15.09.2009)	24 SEP 2009
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

********** SUPPLEMENTAL BOX **********

Continuation of Box III: Lack of Unity of Invention:

The inventions listed as Groups I+ and II+ do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The screening method of Group I+ is not a method of using the claimed compounds.

Groups I+ and II+ share the technical feature of a compound that is capable of activating JNK and inhibiting NF-kappa B. However, this shared technical feature does not represent a contribution over the prior art. Specifically, a paper entitled "Novel Inhibitors of Cytokine-induced IkBa Phosphorylation and Endothelial Cell Adhesion Molecule Expression Show Anti-inflammatory Effects in Vivo" by Pierce et al. (THE JOURNAL OF BIOLOGICAL CHEMISTRY 22 August 1997, 272(34):21096-21103) discloses compounds acting "by inhibiting tumor necrosis factor-a-induced phosphorylation of IkB-a, resulting in decreased nuclear factor-kB and decreased expression of adhesion molecules... Although these compounds exhibited other activities, including stimulation of ... JNK-1..., these effects are probably distinct from the effects on adhesion molecule expression since they were reversible" (Abstract). Pierce et al. further discloses compounds 11-7082 and 11-7085 (Fig 1, pg 21098) that are identical to the claimed compounds of claims 18 and 19, respectively. As the above compounds were known at the time of the invention, they cannot be considered a special technical feature that would otherwise unify the groups.

In addition, Group I+ and Group II+ each lack unity because some of the claimed compounds do not share significant structural similarities, whereas compounds of claims 18-19 or claims 35-36 were known at the time of the invention, as evidenced by Pierce et al. Without significant structural similarities that represent an improvement over prior art, the inventions do not share a special technical feature. Without a shared special technical feature, the inventions lack unity with one another.

Groups I+ and II+ therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: CHRISTOPHER L. CURFMAN
BALLARD SPAHR ANDREWS & INGERSOLL, LLP
SUITE 1000, 999 PEACHTREE STREET, N.E.
ATLANTA, GA 30309

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	24 SEP 2009
Applicant's or agent's file reference 21101.0149P1	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 09/39508	03 April 2009 (03.04.2009)	03 April 2008 (03.04.2008)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 31/10; A61K 31/04; A61K 31/015 (2009.01)
USPC - 514/709; 514/740; 514/764

Applicant UNIVERSITY OF UTAH RESEARCH FOUNDATION

1. This opinion contains indications relating to the following items:

- [x] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [x] Box No. IV Lack of unity of invention
- [x] Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [ ] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	15 September 2009 (15.09.2009)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2009)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 09/39508

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 09/39508

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the appicable time limit:

   ☐ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☒ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I+: claims 1-22, drawn to a method of screening compounds for anticancer activity. The first invention encompasses a method wherein the compound the compound is (E)-(3-methyl)phenyl]-sulfonyl]-2-propennitril). Additional small molecules will be searched for an additional fee. Should Applicant have additional small molecules searched, Applicant must specify them. The exact claims searched will depend on the specifically elected small molecule.

Group II+: claims 23-78, drawn to a composition comprising a JNK activator and NF-kappa B inhibitor, and using said composition. Should Applicant pay an additional fee(s), Applicant must specify small molecules to be searched. The exact claims searched will depend on the specifically elected small molecule.

The inventions listed as Groups I+ and II+ do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The screening method of Group I+ is not a method of using the claimed compounds.

Groups I+ and II+ share the technical feature of a compound that is capable of activating JNK and inhibiting NF-kappa B. However, this shared technical feature does not represent a contribution over the prior art. Specifically, a paper entitled "Novel Inhibitors of Cytokine-induced IkBa Phosphorylation and Endothelial Cell Adhesion Molecule Expression Show Anti-inflammatory Effects in Vivo" by Pierce et al. (THE JOURNAL OF BIOLOGICAL CHEMISTRY 22 August 1997, 272(34):21096-21103) discloses compounds acting "by inhibiting tumor necrosis factor-a-induced phosphorylation of IkB-a, resulting in decreased nuclear factor-kB and decreased expression of adhesion molecules... Although these compounds exhibited other activities, including stimulation of ... JNK-1..., these effects are probably distinct from the effects on adhesion molecule expression since they were reversible" (Abstract). Pierce et al. further discloses compounds 11-7082 and 11-7085 (Fig 1, pg 21098) that are identical to the claimed compounds of claims 18 and 19, respectively. As the above compounds were known at the time of the invention, they cannot be considered a special technical feature that would otherwise unify the groups.

In addition, Group I+ and Group II+ each lack unity becausesome of the claimed compounds do not share significant structural similarities can readily be ascertained, whereas compounds of claims 18-19 or claims 35-36 were known at the time of the invention, as evidenced by Pierce et al. Without significant structural similarities that represent an improvement over prior art, the inventions do not share a special technical feature. Without a shared special technical feature, the inventions lack unity with one another.

Groups I+ and II+ therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

4. Consequently, this opinion has been established in respect of the following parts of the international application:

   ☐ all parts

   ☒ the parts relating to claims Nos. Claims 1-9, 11-18, 20-22, restricted to (E)3-(4-methyl)phenyl]-sulfonyl]-2-propenenitrile

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 09/39508

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	2, 4, 6, 20-22	YES
	Claims	1, 3, 5, 7-9, 11-18	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-9, 11-18, 20-22	NO
Industrial applicability (IA)	Claims	1-9, 11-18, 20-22	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1, 3, 5, 7-9, and 11-18 lack novelty according to PCT Article 33(2) as anticipated by the publication titled "Novel inhibitors of cytokine-induced IkappaB alpha phosphorylation and endothelial cell adhesion molecule expression show anti-inflammatory effects in vivo" by Pierce et al. (hereinafter "Pierce").

As to claim 1, Pierce teaches a method of screening compounds for anticancer activity, comprising:
a. providing a compound (abstract; " We have identified two compounds");
b. assaying the compound for NF-KB inhibitory activity (pg 21096 right col para 2, "In response to TNFa stimulation, IkB-a is phosphorylated on 2 serine residues (Ser-32 and Ser-36), ubiquitinated, and degraded by a proteosome-dependent pathway allowing active NF-kB to translocate to the nucleus where it can activate gene expression"; pg 21096 right col para 3, "Both compounds decreased TNFa-induced nuclear translocation of NF-kB through inhibition of the TNFa-induced phosphorylation of IkB-a");
c. assaying the compound for JNK activation,activity; "pg 21096 right col para 3; "we examined the effects of compound 1 on TNF alpha -induced activity of the stress-activated protein kinases, p38 and JNK-1. This agent increased the activity of p38 kinase and JNK-1");
d. identifying compounds with both NF-KB inhibitory activity and JNK activation activity, the identified compounds having anticancer activity (pg 21096 right col para 2 and 3).

As to claim 3, Pierce further teaches that the NF-kappaB assay and the JNK assay are performed simultaneously (pg 21096 right col para 3; "Compound 1 selectively inhibited the TNFa-inducible phosphorylation of IkB-a without affecting the constitutive IkB-a phosphorylation. To determine whether these agents may inhibit other cellular phosphorylation events, we examined the effects of compound 1 on TNFalpha -induced activity of the stress-activated protein kinases, p38 and JNK-1. This agent increased the activity of p38 kinase and JNK-1").

As to claim 5, Pierce further teaches that the assay of step b assays for indirect NF-KB Inhibition (pg 21096 right col para 2, "In response to TNFa stimulation, IkB-a is phosphorylated on 2 serine residues (Ser-32 and Ser-36), ubiquitinated, and degraded by a proteosome-dependent pathway allowing active NF-kB to translocate to the nucleus where it can activate gene expression"; pg 21096 right col para 3, "Both compounds decreased TNFa-induced nuclear translocation of NF-kB through inhibition of the TNFa-induced phosphorylation of IkB-a").

As to claim 7, Pierce further teaches that the compound comprises an olefin having at leastone electron-withdrawing group (pg 21098 fig 1; compound 1=BAY 11-0782=(E)3-[(4- methylphenyl)-sulfonyl]-2-propenenitrile where electron withdrawing group is sulfo-oxy).

As to claim 8, Pierce further teaches that the compound comprises an olefin having at least two electron-withdrawing groups (pg 21098 fig 1; compound 1=BAY 11-0782, where the 2 electron withdrawing groups are sulfo-oxy and cyano groups).

As to claim 9, Pierce further teaches that the electron-withdrawing group comprises a cyano group, a sulfo-oxy group (pg 21098 fig 1; compound 1).

As to claim 11, Pierce further teaches that the sulfo-oxy group has the structure wherein R1 is substituted aromatic (pg 21098 fig 1; compound 1).

As to claim 12, Pierce further teaches that the compound comprises an olefin having a cyano group and a sulfo-oxy group having the structure wherein R2 is substituted aromatic (pg 21098 fig 1; compound 1).

As to claim 13, Pierce further teaches that the compound or the library of compounds comprises the structure wherein R2, R3 and R4 are, independently, hydrogen, or substituted, wherein the compound is the E-isomer (pg 21098 fig 1; compound 1=BAY 11-0782=(E)3-[(4-methylphenyl)-sulfonyl]-2-propenenitrile).

As to claim 14, Pierce further teaches that R3 and R4 are hydrogen (pg 21098 fig 1; compound 1).
As to claim 15, Pierce further teaches that the R2 is substituted phenyl (pg 21098 fig 1; compound 1).
As to claim 16, Pierce further teaches that the R2 is a phenyl group having at least one alkyl group (pg 21098 fig 1; compound 1).

As to claim 17, Pierce further teaches that the compound is the E-isomer (pg 21098 fig 1; compound 1=BAY 11-0782=(E)3-[(4-methylphenyl)-sulfonyl]-2-propenenitrile).

----------continued in Supplemental Box----------

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 09/39508

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of:
Box V(2):

As to claim 18, Pierce further teaches that the compound comprises the structure (E)3-[(4- methylphenyl)-sulfonyl]-2-propenenitrile (pg 21098 fig 1; compound).

Claims 2, 4 and 6 lack an inventive step according to PCT Article 33(3) as obvious over Pierce, as above, in view of US 2005/0124590 A1 (KUWADA).

As to claim 2, Pierce teaches utilizing HUVEC cells for both the NF-KB assay and/or the JNK assay (pg 21097 left col para 2). Pierce does not teach use of aDLD-1 or HT-29 cancer cell line. However, Kuwada teaches using HT-29 cells in the NF-KB assay (para [0005]; " FIG. I shows the effect of NF-KB inhibitors on colon cancer cell proliferation. DLD-1, HCT-116, and HT-29 were cultured on 96-well plates in the presence or absence of BAY 11-7082"). An artisan of ordinary skill would have readily appreciated that NF-KB is a common transcriptional factor found in many types of cells and therefore many types of cell lines could have been used to measure the effect of drugs on its activities. Consequently, it would have been obvious to one of ordinary skill in the art to combine use of cells in NF-KB assay, as taught by Pierce, with HT-29 or DLD-1 cells specifically, as taught by Kuwada, because many types of cells utilize NF-KB as a transcription factor and therefore could be utilized in an assay.

As to claim 4, Pierce teaches indirect NF-KB inhibition in the assay of step b (pg 21096 right col para 3). Pierce does not teach assay for direct NF-KB inhibition. However, Kuwada teaches assay for direct NF-KB inhibition (claim 53; "wherein the NF-KB inhibitor directly inhibits NF-KB"). An artisan of ordinary skill would have appreciated that some drugs would have inhibited NF-KB indirectly by interfering with its expression or interaction with other molecules while other drugs would have inhibited NF-KB by directly binding to it. Consequently, it would have been obvious to one of ordinary skill in the art to combine assay for NF-KB inhibition, as taught by Pierce, with direct inhibition of NF-KB activity, as taught by Kuwada, because drugs can have either a direct or indirect effect on NF-KB activity.

As to claim 6, Pierce teaches assay (abstract) but does not specifically teach assaying for FLIP activation. However, Kuwada teaches assaying for FLIP activation (para [0240]; "Disclosed herein FLIP was expressed in the DLD-1 and HT-29, but not the HCT-116, cell lines. Twenty uM BAY 11-7085 caused only a slight diminution in the expression of the 54 kilo dalton (long) isoform of FLIP in adherent, but not transiently suspended, HT-29 cells"). A skilled artisan would have readily appreciated the value of assaying for FLIP activity since it antagonizes the effect of TNF alpha in causing apoptosis. Consequently, it would have been obvious to an artisan of ordinary skill in the art to combine assaying cell activity, as taught by Pierce, with assaying for FLIP activation, as taught by Kuwada, because FLIP activation has an antagonistic effect on TNF alpha mediated apoptosis, and because TNF alpha also has an effect on NF-KB activity.

Claims 20-21 lack an inventive step according to PCT Article 33(3) as obvious over Pierce, as above, in view of the publication titled "Suppression of nuclear factor-kappaB and stimulation of inhibitor kappaB by troglitazone: evidence for an anti-inflammatory effect and a potential anti atherosclerotic effect in the obese" by Ghanim et al. (hereinafter "Ghanim").

As to claims 20-21, Pierce teaches compounds with inhibitory activity against NF-kB (abstract). Pierce does not teach wherein the compound comprises a thiazolidinedione or more specifically, troglitazone (a thiazolidinedione). However, Ghanim teaches the thiazolidinedione troglitazone with inhibitory activity against NF-kB (abstract; "To elucidate whether troglitazone exerts an anti-inflammatory effect in humans, in vivo, we investigated the suppression of nuclear factor kB (NFkB) in mononuclear cells (MNC)by this drug"). An artisan of ordinary skill in the art would have readily appreciated that many classes of drugs were known to have NF-kB inhibitory activity. Consequently, it would have been obvious to one of ordinary skill in the art to combine inhibitory activity against NF-kB, as taught by Pierce, with inhibitory activity by the thiazolidinedione troglitazone, because there are many ways to modulate NF-kB activity, including utilizing troglitazone.

Claim 22 lacks an inventive step according to PCT Article 33(3) as obvious over Pierce, as above, in view of the publication titled "Anisomycin Selectively Desensitizes Signaling Components Involved in Stress Kinase Activation and fos and jun Induction" by Hazzalin et al. (hereinafter "Hazzalin").

As to claims 22, Pierce teaches compounds with activation activity of JNK (abstract). Pierce does not teach wherein the compound comprises anisomycin. However, Hazzalin teaches the compound comprises anisomycin (abstract; "Anisomycin, a translational inhibitor secreted by Streptomyces spp., strongly activates the stress-activated mitogen-activated protein (MAP) kinases JNK/SAPK (c-Jun NH2-terminal kinase/stress-activated protein kinase) and p38/RK in mammalian cells"). An artisan of ordinary skill in the art would have readily appreciated that many classes of drugs were known to have JNK activation activity. Consequently, it would have been obvious to one of ordinary skill in the art to combine activation of JNK activity, as taught by Pierce, with activation activity of JNK is anisomycin, as taught by Hazzalin, because there are many ways to modulate JNK activity, including utilizing anisomycin

Claims 1-9, 11-18 and 20-22 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.